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1. Fukumoto Y, Hiro T, Fujii T, et al. Localized elevation of shear stress is related to coronary plaque rupture: a 3-dimensional intravascular ultrasound study with in-vivo color mapping of shear stress distribution. J Am Coll Cardiol 2008;51:645–50.
2. Li ZY, Howarth SP, Tang T, Gillard JH. How critical is fibrous cap thickness to carotid plaque stability? A flow-plaque interaction model. Stroke 2006;37:1195–9.

Reply

We would like to express our gratitude to Drs. Li and Gillard for giving us their honest comments regarding our article (1). The key points of their criticism were: 1) we have to recognize the inherent limitations of computational fluid dynamics; and 2) we should consider the degree of stenosis, pressure distribution across the stenosis, as well as in-plaque stress, all of which may be more important in plaque rupture. We agree entirely with these comments.

Any kind of computational analysis, especially for life systems, requires many assumptions and hypotheses. To ensure its validity, all we can examine is the correspondence between the calculated results and the real-world data. The location of shear stress concentration obtained by our program, which is commercially available, corresponded almost exactly to the real location of plaque rupture. It may be true that the maximum shear stress should be at the location of the maximum stenosis; however, it comes to effect only if the cross-sectional lumen is circular or uniform in shape. The lumen shapes we analyzed were much more complicated, having non-negligible side branches, and the top of plaque hill usually did not correspond to the maximum stenosis. Furthermore, shear stress is dependent on not the peak value but the maximum "derivative" of flow velocity with respect to the distance from the vessel wall. Even if our data did not indicate the real shear stress, our method can still be useful for predicting the future rupture point.

Regarding other critical factors in plaque rupture, such as wall-distending pressure, the degree of stenosis, and in-plaque stresses, we responded to the previous letter to the editor (2). In addition to their work in 2006 (3), we also published an article in the *Journal* in 2005 (4) demonstrating the importance of fibrous cap thickness, lipid core, and calcification in plaque rupture. Wall-distending pressure or in-plaque stress may be much more important in driving the plaque rupture, because the degree of shear stress is very small compared with such forces. Therefore, we think that the local elevation of shear stress might become a trigger rather than a major driving force of plaque rupture. When one attempts to tear a thin paper into 2 parts, just stretching the paper is not sufficient. However, if one makes just a tiny cut in an edge of the paper, it will tear it very easily. We think that the local elevation of shear stress might form such a tiny cut-line, which may be derived from the modification of endothelial cell functions.

In our study (1), we demonstrated just such a statistical relationship between shear stress and plaque rupture. We are under the impression that plaque rupture is a multifactorial multiprocess as well as multi-interaction phenomenon that is deterministic in some ways and stochastic in others.

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Local Blood Pressure Rather Than Shear Stress Should Be Blamed for Plaque Rupture

A recent article (1) published in the *Journal* corroborates the hypothesis that shear stress triggers fibrous cap rupture. In 20 patients with considerable lumen narrowing (maximum area reduction of 80 ± 7%), ulcerative plaque rupture preferentially occurred in areas with locally high wall shear stresses (WSS), estimated by means of computational modeling. However, the authors of this study do not answer the basic question of whether local WSS distribution is indeed related to plaque rupture.

Hemodynamics is an interplay between pressure, flow, and morphology. The study by Fukumoto et al. (1) mainly considers the interaction between flow and morphology under steady-state conditions. Compared with an unaffected site, the increase in WSS around a plaque can be estimated to be a factor of 10 assuming simple circular geometries. For a normal WSS of 0.6 Pa (2), the mean WSS within the stenosis will remain <10 Pa, which might be too low to initiate plaque rupture directly, as acknowledged by the authors.

The article does not fully appreciate the influence of local blood pressure within a stenosis, although this pressure was calculated as well. Let us consider the hemodynamics in the vicinity of a stenosis (3), where in a steady-state situation the sum of potential energy (local blood pressure) and kinetic energy (local blood velocity) is constant (Bernoulli equation): an increase in velocity induced by geometry decreases local pressure (3). An area reduction of 80% converts to an increase in velocity by a factor of 5, and the